Version 18/10/78 DRAFT

Attachment 1

VINYLIDENE CHLORIDE and VINYLIDENE CHLORIDE-VINYL CHLORIDE COPOLYMERS

Vinylidene chloride

1. Chemical and Physical Data

1.1 Synonyms and trade names

Chem. Abstr. Services Reg. No.: 75035-4

Chem. Abstr. Name: 1,1-Dichloroethene

1,1-Dichloroethylene; *asym*-dichloroethylene

Sconatex

1.2 Structural and molecular formulae and weight

$C_2H_2Cl_2$ Mol. wt: 97.0

1.3 Chemical and physical properties of the pure substance

From Weast (1976), unless otherwise specified

(a) Description: Clear liquid with a sweet odour (Hardie, 1964; Windholz, 1976)

(b) Boiling-point: 37°C

(c) Melting-point: -122.1°C

(d) Density: d^{20} 1.218; vapour density ~~at 37°C~~, 3.4 (air = 1) (Anon., 1972)

(e) Refractive index: n_D^{20} 1.4249

(f) Spectroscopy data: λ vapour <200 nm; infra-red, nuclear magnetic resonance, and mass spectral data have been tabulated (Grasselli & Ritchey, 1975)

(g) Solubility: Insoluble in water (0.04% wt/vol. at 20°C); miscible with most organic solvents (Hardie, 1964)

25018033

CMA 014064

BFG61189

(h) Volatility: Vapour pressure is 400 mm at 14.3°C (Perry & Chilton, 1973)

(i) Stability: Flash-point (closed cup), -17°C (Anon., 1972); easily polymerized at temperatures above 0°C in the presence of oxygen or other catalysts (Windholz, 1976)

(j) Conversion factor: 1 ppm in air is approximately 4 mg/m³

1.4 Technical products and impurities

Vinylidene chloride is commercially available in the US with the following typical specifications: vinylidene chloride, 99.6 wt %; acetylene, 25 mg/kg max.; other chlorinated hydrocarbons, none exceeding 0.25 wt %; acidity (as hydrogen chloride), 10 mg/kg max.; peroxide (as hydrogen peroxide), 10 mg/kg max.; water, 50 mg/kg max.; and inhibitor (monomethyl ether of hydroquinone), 180 to 220 mg/kg (PPG Industries, 1975).

Typical specifications for vinylidene chloride produced in Japan are as follows: specific gravity (d_4^{20}), 1.2129; melting-point, -122.1°C; boiling-point, 33.4°C; and refractive index (n_D^{20}), 1.4249.

2. Production, Use, Occurrence and Analysis

2.1 Production and use

(a) Production

Vinylidene chloride was first prepared by Regnault in 1838 by the reaction of trichloroethane and alcoholic potassium hydroxide (Reinhardt, 1943).

Although vinylidene chloride may be prepared by several methods, it is commercially produced in the US and Japan by the dehydrochlorination (using sodium hydroxide or lime) of 1,1,2-trichloroethane, derived from ethylene dichloride. The resulting crude vinylidene chloride is purified by washing, drying, and fractional distillation. Inhibitors are normally added at this point (Weesling & Edwards, 1971).

The commercial production of vinylidene chloride was dependent on the development and commercialization of vinylidene chloride copolymers, and was first reported in the US in 1940 (US Tariff Commission, 1941).

It is estimated that two US companies produced a combined total of 70 million kg vinylidene chloride in 1976 and that one of these companies manufactured an additional 50 million kg for captive use as an unisolated intermediate in the production of 1,1,1-trichloroethane. US imports and exports of vinylidene chloride are negligible.

Vinylidene chloride has been produced commercially in Japan since 1951. In 1976, three companies produced a combined total of 28.1 million kg. Japanese imports and exports of vinylidene chloride are negligible.

(b) Use

Excluding the amount used as an unisolated intermediate in the production of 1,1,1-trichloroethane, more than 90% of the vinylidene chloride produced in the US and Japan is used in the production of copolymers of high vinylidene chloride content, the other major monomer usually being vinyl chloride. For a discussion on the uses of vinylidene chloride-vinyl chloride copolymers and other vinylidene chloride-based polymers, see p. .

The remaining 10% or less of the vinylidene chloride produced is used in the manufacture of modacrylic fibres, which are largely based on acrylonitrile with small amounts of vinylidene chloride and other monomers. For a discussion on the uses of these fibres, see "Acrylic and modacrylic fibres", p. .

The American Conference of Governmental Industrial Hygienists (ACGIH) recommends that an employee's exposure to vinylidene chloride does not exceed an eight-hour time weighted average of 40 mg/m^3 (10 ppm) in the workplace air in any eight-hour work shift of a forty-hour work week. During any fifteen minute period, the ACGIH proposes an absolute ceiling concentration limit of 80 mg/m^3 (20 ppm) provided the daily threshold limit value (in terms of eight-hour time weighted values) is not exceeded (ACGIH, 1976).

2.2 Occurrence

Vinylidene chloride is not known to occur as a natural product.

(a) Air

Workers involved in manufacturing facilities using vinyl chloride in polymerization processes (e.g., polyvinyl chloride) have been reported to be exposed to vinylidene chloride concentrations (Jaeger, 1976; Ott *et al.*, 1975) in amounts of less than 20 mg/m^3 (5 ppm) and most frequently to trace amounts (Kramer & Mutchler, 1972). Vinylidene chloride at levels of 8 mg/m^3 (2 ppm) has also been reported to be a contaminant of submarine and at levels of 0-2 ppm of spacecraft atmospheres (Altman & Dittmer, 1966).

Emissions of vinylidene chloride in the US in 1974 have been estimated at 1.52 million kg from monomer synthesis operations (reduced to 277 thousand kg by new control technology in late 1975), 308 thousand kg from polymer synthesis operations, and 13.8 thousand kg from polymer fabrication operations (Rushon & Kommreich, 1976).

(b) Water

Vinylidene chloride has been detected in effluent discharged from chemical manufacturing plants in The Netherlands at a concentration of 32 µg/l (Eurocop-Cost, 1976) and in effluent discharged by chemical and latex manufacturing plants in the US. It has also been identified in well, river, and raw water in the US (Shackelford & Keith, 1976). The highest reported concentration of vinylidene chloride in the US finished drinking water was 0.1 µg/l (US Environmental Protection Agency, 1975).

(c) Other

Vinylidene chloride has been found as an impurity in trichloroethylene (retention volume: 0.192) (Valisov & Bodyagin, 1970), in vinyl chloride monomer (limit of detection, 5 mg/kg) (Kiezal *et al.*, 1975; Sassu *et al.*, 1968), and at a level of 0.011% in commercial chloroprene (Rurginyan & Shirinyan, 1969).

Commercial household and industrial saran films have been analyzed for residual vinylidene chloride monomer. Six rolls of household film had

monomer concentrations ranging from 6.5 to 10.4 mg/kg, with an average of 8.8 mg/kg. There were no significant differences in samples taken from the beginning (outside) or the end (inside) of each roll. The industrial film showed levels ranging from 10.8 to 26.2 mg/kg with levels increasing from the beginning to the end of the roll (Birkel *et al.*, 1977).

2.3 Analysis

Vinylidene chloride has been identified in air by trapping in pyridine and colorimetric determination of the cyanine obtained by reaction with barbituric acid or aniline. The limit of detection was 10 mg/m^3 (2.5 ppm) (Gronsberg, 1975).

Gas chromatography has been used to determine vinylidene chloride as an impurity (1) in trichloroethylene (Vlasov & Bodyagin, 1970) and (2) in vinyl chloride monomer (Sassu *et al.*, 1968) with a limit of detection of 5 mg/kg (Kiezel *et al.*, 1975). The same thod has been applied to the detection of free vinylidene chloride in latex (Bollini *et al.*, 1974).

Sampling techniques using activated carbon as adsorbet with subsequent solvent or thermal desorption and gas chromatographic analysis have been evaluated to determine vinylidene chloride in industrial atmospheres (Severs & Skory, 1975). A sampling technique for concentration of air pollutants including vinylidene chloride on different gas chromatography has been evaluated. The compounds were thermally desorbed and analyzed by gas chromatography using flame ionization detection: the limit of detection is 4 µg/m^3 (1 ppb) (Russell, 1975).

Vinylidene chloride has been detected in saran films by gas chromatography with electron capture detection and mass spectrometry confirmation. The limit of detection of the method is 5 mg/kg (Birkel *et al.*, 1977).

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity and related studies in animals[1]

(a) Oral administration

Rat: In a preliminary report of an ongoing study, groups of 50 male and 50 female Sprague-Dawley rats were administered 5, 10 or 20 mg/kg bw vinylidene chloride in olive oil by stomach tube once daily, 4-5 days/week, for 52 weeks; 1 carcinoma of the Zymbal gland was observed in a rat treated with the 10 mg/kg bw dose. A control group of 100 male and 100 female rats were given olive oil alone. At the time of reporting, the rats had been observed for 93 weeks after the start of treatment (Maltoni *et al.*, 1977).

(b) Inhalation exposure

Mouse: In an experiment still in progress at the time of reporting, groups of Swiss mice, 9 or 16 weeks of age, were exposed 4 hours/day, 4-5 days/week, to vinylidene chloride vapours in air at concentrations of 800, 400, 200, 100, or 40 mg/m^3 (200, 100, 50, 25 or 10 ppm). Due to toxicity, mice treated with 200 (60 males and 60 females) or 100 ppm (30 males and 30 females) were exposed for only 2 days and those treated with 50 ppm (30 males and 30 females) for one week only . At the 25 ppm level, 30 males and 30 females were initially exposed and a further group of 120 male and 120 female mice was started at the same exposure level and treatment of both groups continued for 52 weeks; at the time of reporting, 98 weeks, 24/150 males and 1/150 females had developed adenocarcinomas of the kidney, often bilateral. One male had a kidney adenocarcinoma in the group treated with 50 ppm for one week. No such tumours had occurred in mice exposed to 10 ppm for 52 weeks or in 380 controls (both groups observed until 98 weeks of age) (Maltoni, 1977; Maltoni *et al.*, 1977).

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[1]The Working Group was aware of ongoing studies to assess the carcinogenicity of vinylidene chloride in mice by skin application and s.c. injection and in mice and rats by oral administration (IARC, 1978). The Working Group was also aware of ongoing oral (drinking-water) and inhalation studies using rats in which the data analysis was not complete (Rampy *et al.*, 1977). Further inhalation studies on two strains of rats were also incomplete (Viola & Caputo, 1977).

A group of 36 male and 36 female CD-1 mice, 2 months of age, were exposed to 220 mg/m^3 (55 ppm) vinylidene chloride in air 6 hours/day, 5 days a week for 12 months, at which time the experiment was terminated. Two males died early in the experiment and were replaced by healthy mice; 2 males were killed in the 9th month of treatment and one female during the 10th month of treatment. Bronchiolo-alveolar adenomas occurred in 6 mice and angiosarcomas of the liver occurred in 3 mice treated with vinylidene chloride; no such tumours occurred in controls. Three hepatomas and 2 skin keratoacanthomas were also reported to occur in treated mice (Lee *et al.*, 1977, 1978) [The Working Group noted the short duration of the experiment].

Rat: A group of 36 male and 36 female CD rats were exposed to vinylidene chloride in air at a concentration of 220 mg/m^3 (55 ppm) 6 hours/day, 5 days a week for up to 12 months, at which time the experiment was terminated and all survivors killed. Two rats developed angiosarcomas, one in the mesenteric lymph node and one in the subcutaneous tissue. Such tumours did not occur in controls (Lee *et al.*, 1977, 1978) [The Working Group noted the short duration of the experiment].

One group of 60 male and 60 female Sprague-Dawley rats were exposed to 800 reduced to 600 mg/m^3 (200 reduced to 150 ppm), and 4 groups of 30 female and 30 male Sprague-Dawley rats were exposed to 40, 100, 200 or 400 mg/m^3 (10, 25, 50 or 100 ppm) vinylidene chloride in air for 4 hours/day, 4-5 days a week for 52 weeks and observed for up to 82 weeks (time of reporting). The animals were 16 weeks old at the start of treatment. An increased incidence of mammary fibroadenomas and carcinomas (40-60%) was reported when compared with 100 male and 100 female controls (32%). No dose-response relation was found. In addition, one Zymbal gland carcinoma was seen in one rat treated with the 100 ppm dose (Maltoni *et al.*, 1977).

Hamster: In a study still in progress, no tumours had occurred at 74 weeks among a group of 30 male and 30 female Chinese hamsters, 28 weeks of age, exposed to 25 ppm vinylidene chloride in air 4 hours/day, 4-5 days a week for 52 weeks (Maltoni *et al.*, 1977).

3.2 Other relevant biological data

The adverse biological effects of vinylidene chloride have been reviewed (EPA, 1976; Haley, 1975; Warren & Ricci, 1978).

(a) Experimental systems

Toxic effects

Results reported for acute toxicity studies on vinylidene chloride have been highly variable, the lethal concentrations are dependent on the dietary parameters (fed or fasted animals) and on the hepatic glutathione content which exhibited significant variations in diurnal rhythm (Jaeger *et al.*, 1973a, 1974). The LC_{50} by inhalation for a 4 hour exposure was 40-60 mg/l (10,000-15,000 ppm) in fed rats and 2-10 mg/l (500-2500 ppm) in fasted rats (Jaeger *et al.*, 1973b); the minimum lethal concentration was 10,000 ppm for a 24 hour exposure for fed rats (Jaeger *et al.*, 1974). The LC_{50} of vinylidene chloride for rats following exposure for 4 hours and observation for 2 weeks was 25.4 mg/l (6350 ppm) (Siegel *et al.*, 1971). The oral LD_{50} in mice was 200 mg/kg bw (Jones & Hathway, 1978a). The oral LD_{50} was 1500 mg/kg bw in normal rats and 80 mg/kg bw in adrenalectomized rats (Jenkins *et al.*, 1972). In dog, the oral minimal lethal dose was 5750 mg/kg bw and the i.v. minimal lethal dose was 225 mg/kg bw. The s.c. minimal lethal dose in rabbits was 3900 mg/kg bw (Barsoum & Saad, 1934). Death was due to vascular collapse and shock (Jaeger *et al.*, 1973b).

Inhalation studies using rats, guinea-pigs, dogs, rabbits and monkeys with exposures at mean level of 189 mg/m^3 (48 ppm) for 90 days produced significant mortality and liver damage but no changes in haematological parameters (Prendergast *et al.*, 1967). Inhalation of vinylidene chloride for 20 6-hour exposures at 2 mg/l (500 ppm) caused nose irritation, reduced weight gain and hepatic histopathological changes in rats (Gage, 1970). In fasted rats exposed to 0.8 mg/l (200 ppm) for 4 hours, liver parenchymal cell injury was observed (Reynolds *et al.*, 1975).

Minimal liver changes characterized by an increase in cytoplasmic vacuolization of occasional individual hepatocytes were noted in Sprague-Dawley rats treated with 6-8 mg/kg bw/day for 90 days vinylidene chloride

given at a concentration of 200 mg/l in their drinking-water. In a status report on a two-year study with male and female Sprague-Dawley rats receiving 16-40 mg/kg bw/day (200-230 mg/l), 8-20 mg/kg bw/day (100-120 mg/l) and 5-12 mg/kg bw/day (60-70 mg/l) in their drinking-water, no toxicological effects were noted except for a non-dose related decrease in survival of male rats only at 18 and 24 months. Rats exposed for 30 or 90 days to doses of 0.1-0.3 mg/l (25-75 ppm) in air showed minimal toxicological effects in the liver (Norris, 1977).

Vinylidene chloride affects the activity of several liver enzymes, notably it decreases hepatic glucose-6-phosphatase and increases serum alanine α-ketoglutarate transaminase (SAKT). It increases the liver content of triglycerides and decreases that of glutathione. Decreased hepatic glutathione concentrations increase the lethality and hepatotoxicity of vinylidene chloride (Jaeger *et al.*, 1973a,c). The microsomal enzyme inducers, phenobarbital and 3-methylcholanthrene, increased the lethality of vinylidene chloride inhalation (Carlson & Fuller, 1972).

Vinyl chloride, when administered simultaneously with vinylidene chloride, prevented the injury associated with vinylidene chloride inhalation in fasted rats (Jaeger, 1975).

Various epoxides (1,1,1-trichloropropane-2,3-oxide; 2,3-epoxypropan-1-ol; styrene oxide; butadiene monoxide; and cyclohexene oxide) enhanced the hepatotoxicity of vinylidene chloride in male rats and decreased the acute oral LD_{50} (Andersen & Jenkins, 1977).

Embryotoxicity and teratogenicity

Rats were given vinylidene chloride either as 200 mg/l in the drinking-water or as 20-160 ppm (80-640 mg/m^3) 7 hours/day by inhalation on days 6-15 of gestation. Rabbits were given the same dose by inhalation on days 6-18 of gestation. No teratogenic effect was seen both in rats or rabbits. Some evidence of embryotoxicity or foetotoxicity was observed in both rats and rabbits exposed to vinylidene chloride by inhalation; these effects were associated with maternally toxic levels of exposure (Norris, 1977).

Absorption, distribution, excretion and metabolism

In rats, as the dose level of radioactive vinylidene chloride is increased from 1-50 mg/kg bw oral, or from 0.04-0.8 mg/l (10-200 ppm) inhalation, the metabolic pathway becomes saturated so that percentage-wise, less of the dose administered is metabolized and more is eliminated *via* the lungs as vinylidene chloride. At the 1 mg/kg bw oral dose and the 10 ppm inhalation dose, there was no difference in elimination by fed *versus* fasted rats. At 50 mg/kg bw oral or 200 ppm inhalation, there was a significant increase in the excretion of vinylidene chloride *via* the lungs and decrease in urinary excretion of radioactivity in fed *versus* fasted rats (Norris, 1977). The main eliminative route for ^{14}C-vinylidene chloride after intragastric, i.v. or i.p. administration to rats is pulmonary; both unchanged vinylidene chloride and related CO_2 are excreted by that route and other vinylidene chloride metabolites *via* the kidneys. Biotransformation of vinylidene chloride gives thiodihydroxyacetic acid and an *N*-acetyl-*S*-cysteinylacetyl derivative as major urinary metabolites together with substantial amounts of chloroacetic acid, dithiohydroxyacetic acid and thiohydroxyacetic acid (Jones & Hathway, 1978b).

Mice metabolize a greater proportion of an oral dose of 50 mg/kg bw vinylidene chloride than rats. Mice (but not rats) excrete a small amount of *N*-acetyl-*S*-(2-carboxymethyl)cysteine and they excrete more *N*-acetyl-*S*-cysteinylacetyl derivative than do rats (Jones & Hathway, 1978a).

Metabolic conversion of vinylidene chloride into an epoxide which can rearrange to the correspondant acyl chloride has been proposed (Henschler, 1978; Jones & Hathway, 1978a,b).

Mutagenicity and other short-term tests

Vinylidene chloride at concentrations of 2% and 20% (20,000-200,000 ppm) in air produced reverse mutations in *Salmonella typhimurium* TA100 and TA 1530 in the presence of 9000 g supernatant from liver, lung and kidneys of mice and rats (Bartsch *et al.*, 1975) and in one human liver specimen (Bartsch *et al.*, 1976). At a concentration of 5% (50000 ppm) in air, it is mutagenic in *S. typhimurium* TA1535 in the presence of a S-9 mix of liver or kidney from mice and rats pretreated with Aroclor 1254. It was weakly mutagenic in the presence of a S-9 mix of liver from a human subject who had been receiving long-term phenobarbital medication (Jones & Hathway, 1978c). Reverse mutations were induced in *Escherichia coli* K 12 by vinylidene chloride solution in the presence of liver microsomes from urine pretreated with phenobarbital (Greim *et al.*, 1[illegible]

Vinylidene chloride was not mutagenic in the dominant lethal test in male CD-1 mice exposed by inhalation to 40, 120 and 200 mg/m^3 (10, 30 and 50 ppm) for 6 hours/day for 5 days (Anderson *et al.*, 1978).

(b) Humans

Acute exposure to high concentrations of vinylidene chloride in air results in central nervous system depression and narcosis. Repeated exposures to low concentrations is associated with liver and renal dysfunction. Skin contact with vinylidene chloride causes irritation which may be partly due to the hydroquinone monomethyl ether inhibitor. Contact with the eye causes conjunctivitis and transient corneal injury (Irish, 1963).

3.3 Case reports and epidemiological studies

Ott *et al.* (1976) investigated the cancer risk among a cohort of 138 workers exposed to vinylidene chloride where vinyl chloride was not used as a copolymer. The authors reported that there were no findings statistically related or individually attributed to vinylidene chloride exposure in this cohort [The Working Group noted that because 27 workers were lost to follow-up but considered alive in the analyses, and that because 55 people had less than 15 years since first exposure and only 5 deaths were observed, these factors preclude any judgement on the findings].

Vinylidene chloride-vinyl chloride copolymers

1. Chemical and Physical Data

1.1 Synonyms and trade names

Chem. Abstr. Services Reg. No.: 9011-06-7

Chem. Abstr. Name: 1,1-Dichloroethene polymer with chloroethene

Chloroethylene-1,1-dichloroethylene polymer; 1,1-dichloroethylene-monochloroethylene polymer; 1,1-dichloroethylene polymer with chloroethylene; vinyl chloride copolymer with vinylidene chloride; vinyl chloride-1,1-dichloroethylene copolymer; vinyl chloride-vinylidene chloride copolymer; vinyl chloride-vinylidene chloride polymer; vinylidene chloride-vinyl chloride polymer

Breon 202; Breon CS 100/30; Daran; Daran CR 6795E; Dow 874; Dow Latex 874; ET 67; Geon 222; Geon 652; IKhS 1; KhS 596; Kurehalon AO; Laplen; Latex SVKh; Polyco 2611; QX 2168; Saran 683; Saran 746; Saran Resin 683; SP 489 SVKh 1; SVKh 40; UP 925; Velon; VIKh 65; Viniden 60; VKhVD 40; Winiden 60

1.2 Structural and molecular formulae and molecular weight

in combination with

$(C_2H_2Cl_2)_x$- $(C_2H_3Cl)_y$ Mol. wt: 10,000 to 100,000

1.3 Chemical and physical properties of the copolymer

(a) Description: Crystalline or amorphous powder depending upon the content of vinylidene chloride (Anon., 1973)

(b) Melting-point: 183-195°C (Wessling & Edwards, 1971)

(c) Solubility: Soluble in tetrahydrofuran, 1,4-dioxane, cyclohexanone, cyclopentanone, chlorobenzene, and dichlorobenzene (Wessling & Edwards, 1971).

(d) Stability: Resistant to sunlight and weathering; γ-rays cause cross linking and chain scission (Wessling & Edwards, 1971)

1.4 Technical products and impurities

Vinylidene chloride-vinyl chloride copolymers are commercially available in the US in several forms: resins, latexes, films, and fibres. The identity and amount of impurities in these products are not available. In general, products obtained by emulsion polymerization (i.e., latexes) have varying amounts of additives used in the polymerization process, such as initiators, activators, and surface-active agents.

The vinylidene chloride-vinyl chloride copolymers commercially available in Japan are believed to be based on 80-90% vinylidene chloride units.

2. Production, Use, Occurrence and Analysis

2.1 Production and use

(a) Production

The polymerization of vinylidene chloride was first observed by Regnault in 1838. During the 1930's in the US, the commerical development of the polymer began. The pure homopolymer is difficult to fabricate because its softening point is very close to its decomposition point. The discovery that inclusion of small amounts of other monomers lowered the softening point led to the commercial introduction in 1940 in the US of the family of vinylidene chloride copolymers now known as saran (Gabbett & Smith, 1964). The copolymers presently of commercial interest in the US are: vinylidene chloride-vinyl chloride (Saran B), vinylidene chloride-alkyl acrylate (Saran C), and vinylidene chloride-acrylonitrile (Saran F). Because saran has now come to be a generic term in the US for copolymers of high vinylidene chloride content, and because these copolymers are also often referred to as simply 'polyvinylidene chloride', the composition of the copolymers described in the literature is not always known.

Vinylidene chloride-vinyl chloride copolymers are presently produced in the US by free radical processes emulsion or suspension. In Japan, they are produced by an emulsion process. The emulsion process produces a polymer latex which can be used directly (usually with additional stabilizing ingredients) or the polymer can be recovered, usually by coagulation with an electrolyte, followed by washing and drying. The emulsion process has the advantage of producing a higher molecular weight polymer than the suspension process and the disadvantage of the relatively high concentration of additives which may affect some of the properties of the polymer. Suspension polymerization is usually used for copolymers used as moulding and extruding resins.

Four US manufacturers now produce vinylidene chloride-vinyl chloride copolymer resins, latexes, and films, and one manufacturer produces vinylidene chloride-vinyl chloride fibre. US production of vinylidene chloride copolymers in 1977 has been estimated at 68 million kg (Anon., 1977).

Vinylidene chloride-vinyl chloride copolymers were first produced commercially in Japan in 1951. In 1976, four Japanese companies produced an estimated 31.9 million kg vinylidene chloride-vinyl chloride copolymers, 2.7 million kg of which was fibre and the remainder, latex and film.

(b) Use

Vinylidene chloride-vinyl chloride copolymers have gained wide use due to their barrier properties to water and gases, their resistance to oil, grease, chemicals, and sunlight, their flexibility, and their heat sealability. In addition, the high chlorine content imparts fire retardancy to the product.

Vinylidene chloride-vinyl chloride copolymers are used in the form of films for food packaging (the largest use); coatings for cellophane, paper and other surfaces; fibres; and tubes and pipes.

Applications for vinylidene chloride-vinyl chloride copolymers in food packaging include: household food wrap; industrial food wrap for drum liners, cheese, luncheon meat, and sausage; shrink film for beef, poultry, and cheese; and in laminations for cap liners, cosmetics, and luncheon meat. A relatively new use is in a coextruded multi-layered film of polyethylene on a vinylidene chloride-vinyl chloride copolymer core (Roth, 1976).

Vinylidene chloride-vinyl chloride copolymers are used as coatings in many applications, and as such are used in two forms: solvent-soluble resins, and water dispersions or latexes.

The solvent-soluble resins are used to coat other polymer films such as cellophane (the largest single application), paper drinking cups and plates, and paperboard cartons. Other uses include interior coatings for ship tanks, railroad tank cars, and fuel storage tanks, coatings for steel piles and structures, binders in coatings for magnetic tapes, audio tapes, video tapes, and computer tapes (Roth, 1976; Wessling & Edwards, 1971).

The latexes are used for coating paper for use in packaging potato chips, pretzels, cereal, and cake mixes, for coating polypropylene and other plastics for packaging and for single serving containers; and for coating paperboard for packaging candy, baked goods, and frozen and refrigerated items. Other applications include use as binders for paints and nonwoven fabrics and as an additive to cement to make high-strength mortars and concretes (Roth, 1976; Wessling & Edwards, 1971).

Extruded fibres made from vinylidene chloride-vinyl chloride copolymer resins are used in a wide variety of applications where resistance to sunlight and chemicals is required (e.g., automotive seat covers, outdoor furniture, agricultural shade cloth, and filter fabrics) (Wessling & Edwards, 1971).

Vinylidene chloride-vinyl chloride copolymer resins are also extruded into tubes, rods, pipes, and pipe liners for use in contact with chemicals and other corrosive media (Wessling & Edwards, 1971).

The multi-layered film of polyethylene on a core of vinylidene chloride-vinyl chloride copolymer reportedly has found use in ostomy devices (Roth, 1976).

In Japan, approximately 8% of the vinylidene chloride-vinyl chloride copolymers produced are in the form of fibres used for fishing nets, interior furnishings, and construction appliances. Approximately 75% are used in film applications, 13% in latex applications, and 4% in other unspecified applications.

The US Food and Drug Administration permits the use of vinylidene chloride copolymers (including the copolymers with vinyl chloride) as components of the following products when they are intended for use in contact with food: (1) adhesives; (2) resinous and polymer coatings; (3) paper and paperboard; (4) rigid and semirigid acrylic and modified acrylic plastics; (5) polyethylene phthalate polymers; and (6) packaging material for use during the irradiation of prepackaged foods (US Food and Drug Administration, 1977).

2.2 Occurrence

Vinylidene chloride-vinyl chloride copolymers are not known to occur as natural products.

2.3 Analysis

The analytical chemistry of vinyl polymers, including vinylidene chloride-vinyl chloride copolymers has been reviewed (Cobler *et al.*, 1968). Methods of detecting surface finishing agents, such as vinylidene chloride polymers, on paper have been reviewed (Proksch, 1969).

Methods of identifying polymer films, including vinylidene chloride copolymers, based on physical and chemical properties have been described (Briston, 1974; Van Gieson, 1969).

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity and related studies in animals

No data were available to the Working Group.

3.2 Other relevant biological data

(a) Experimental systems

Rats fed a diet containing 5% vinyl chloride-vinylidene chloride copolymer for two years showed no toxic effects. Two dogs fed a diet containing 5% of the copolymer were also without evidence of toxic effects (Wilson & McCormick, 1954).

Rabbits treated for three months i.v. with 1 ml/kg bw 1% solution of vinylidene chloride-vinyl chloride copolymer exhibited hypertrophy of the reticulo-endothelial cells of the spleen, bone marrow, liver, lymphatic tissue and lungs (Miyasaki, 1959).

(b) Humans

One case of contact dermatitis, limited to the area of its application, has been reported from the use of Saran Wrap (a vinylidene chloride-vinyl chloride copolymer). A positive patch test to the copolymer was also obtained (Osbourn, 1964).

Two workers developed persistent cranial nerve disorders after cleaning-out tank cars in which an aqueous dispersion of vinylidene chloride copolymers had been transported. These were attributed to trace reaction products found in the copolymer (i.e., monochloroacetylene and/or dichloroacetylene). The trigeminal nerve was principally involved, and to a lesser degree the occipital auricular and cervical cutaneous nerves as well as the muscles of mastication, the eye muscles and the hypoglossus (Henschler *et al.*, 1970).

3.3 Case reports and epidemiological studies

No data were available to the Working Group.

4. Summary of Data Reported and Evaluation

4.1 Experimental data

Vinylidene chloride has been tested by oral administration in rats and by inhalation exposure in mice, rats and hamsters. When given by inhalation in rats and mice, it induced malignant tumours, including angiosarcomas. The preliminary results of another inhalation study in rats and mice indicate the induction of malignant tumours of the kidney in mice, mostly males, and of an increased incidence of mammary tumours in rats. No carcinogenic effect was observed in an on-going study in hamsters exposed to vinylidene chloride by inhalation. The oral study in rats is still underway and cannot be evaluated.

Vinylidene chloride is mutagenic.

No data on the carcinogenicity of vinylidene chloride-vinyl chloride copolymer were available to the Working Group.

4.2 Human data

The production volume of vinylidene chloride is high, and the material is utilized almost entirely in the production of the copolymers. This suggests that occupationally exposed groups might be identified for epidemiological investigation. Production of the vinylidene chloride-vinyl chloride copolymer is extensive, and its use in consumer products (including food packaging) indicates the possibility of widespread human exposure.

The only epidemiological study available to the Working Group reported no tumours associated with exposure to vinylidene chloride, but the data were not adequate to permit an assessment of carcinogenicity.

No case reports or epidemiological studies relevant to the carcinogenicity of vinylidene chloride-vinyl chloride copolymers were available to the Working Group.

4.3 Evaluation

The single epidemiological study on vinylidene chloride available to the Working Group was not adequate to permit an assessment of human carcinogenicity.

In view of the substantial volume of vinylidene chloride manufactured, the use of this compound in copolymers, the identification of the material in industrial emissions and in drinking water, and its presence in some trichloroethylene, some chloroprene, and in household materials, the lack of human epidemiological studies is serious.

The available experimental evidence of carcinogenicity of vinylidene chloride indicates that it produces malignant tumours in mice and rats and that some of the tumours are similar to those produced by vinyl chloride. This evidence is, however, limited by the fact that it is partly based on studies which were still in progress. An evaluation of the carcinogenicity of vinylidene chloride will be made upon completion of studies known to be underway.

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DRAFT

1. Introduction

The present report deals primarily with the results of a project of integrated research designed to study the long-term effects (toxic and carcinogenic) of vinylidene chloride (VDC). The project included several experiments, in which the monomer was administered by different routes (inhalation and ingestion) at different concentrations, on three animal species (Sprague-Dawley rats, Swiss mice and Chine hamsters). To our knowledge, this project, sponsored by several European producers of vinylidene choride --European Study Group for VDC Toxicity (BASF AG, Dow Chemical Europe SA, I.C.I. Ltd, and Solvay et Cie) -- represents the most comprehensive study available in this area.

Moreover, in this report available studies on long-term carcinogenicity bioassays, as well as on other biological parameters concerning the behaviour and effects of VDC, performed in other laboratories and in ours, are reviewed for a better understanding of the biological action of the monomer.

2. Vinylidene chloride

Vinylidene chloride (VDC), or 1,1-dichloroethylene, $CH_2=CCl_2$, is produced in the U.S.A., Japan, and several Western European countries.

Vinylidene chloride is mainly employed for the production of poly(vinylidene chloride) (PVDC) resins and dispersions. Examples are Diofan® (BASF), Ixan® (Solvay), Saran® (Dow), and Viclan® (ICI). The most important property of PVDC is its low permeability to oxygen and moisture.

The major use of PVDC is in the manufacture of flexible packaging for food.

The following population groups may be potentially exposed to VDC: (1) workers engaged in the production of VDC monomers; (2) workers manufacturing and processing VDC polymers on an industrial scale; (3) residents around factories producing VDC and VDC polymers; and, to a much lesser extent, (4) poeple undergoing contact with resins made with VDC and with materials containing these resins and (5) consumers of food preserved in packaging materials coated with VDC resins.

3. History

Up to 1974 no data were available on long-term effects of VDC.

In October 1974, at the XIth International Cancer Congress, held in Florence, Viola reported that he had observed cases of abdominal reticulosarcomas in a group of Wistar rats exposed to VDC by inhalation 4 hours daily, 5 days weekly, at 200 ppm for 5 months and subsequently at 100 ppm for 7 months. At the "Conference on Comparative Metabolism and Toxicity of Vinyl Chloride Related Compounds" held at the National Cancer Institute in Bethesda in May 1977. Viola and Caputo (1977) reported in detail the results of this experiment and moreover the results of a further experiment in which VDC was tested on Sprague-Dawley rats, at 100 ppm and 75 ppm, under the same experimental conditions. The authors concluded:

> "A final statement of the pathological results must await the completion of the microscopic examination of the tissues and organs of all animals. Nevertheless, it seems clear that there is no grossly observable correlation between tumour formation and VDC inhalation."

On the basis of Viola's communication in 1974 The European producers of vinylidene chloride asked our Institute and Tumour Centre to undertake the present project of long-term carcinogenicity bioassays on VDC, which was started in the spring of 1975. From the start of the experiment it was immediately apparent that mice were more sensitive to the acute effects of VDC than rats, and male more than female mice (Maltoni et al., 1975).

At the beginning of 1977, in a series of reports (at the Accademia dei Lincei, Rome; at the International PVDC Seminar of TAPPI, Hamburg; at the American Cancer Society, New York; and at International Agency for Research on Cancer, Lyons), we reported that under our experimental conditions VDC produced kidney adenocarcinomas in male Swiss mice. These early results were then published in full (Maltoni et al., 1977 a, b).

In 1977 the interim results of a two-year toxicological study on the effects on rats of vinylidene chloride incorporated in their drinking water or administered by repeated inhalation, performec at the Toxicology Research Laboratory of Dow Chemical (Midland, USA), were given (Norris, 1977; Ramply et al., 1977).

The research plan and results of the Dow studies were summarized as follows:

> "Male and female Sprague-Dawley rats were exposed to vinylidene chloride (VDC) orally or by inhalation in two-year toxicological studies. VDC was given in the drinking water at mean ± S.D. concentrations of zero, 68 ± 13 ppm, 106 ± 22 ppm, and 220 ± 35 ppm, which produced mean ± S.D. dosage levels of zero, 5.9 ± 0.6 mg/kg, 10.0 ± 1.2 mg/kg, and 19.3 ± 2.7 mg/kg for male rats and zero, 7.5 ± 0.4 mg/kg,

12.6 ± 1.1 mg/kg, and 25.6 ± 2.4 mg/kg for female rats. Forty-eight rats/sex/VDC level and 80 rats/sex in the control group were used in the two year study with an interim kill of an additional 10 rats/sex/level at 90 days. In the inhalation study, rats were exposed to 0, 10 or 40 ppm of VDC vapour 6 h/day, 5 days/week for 5 weeks, after which the exposure levels were changed to 0, 25, and 75 ppm of VDC. Exposure continued for a total of 18 months and the rats held for observation and additional 6 months. Interim kills occurred at 1, 6 and 12 months. A separate 90-day study using 20 rats/sex/level was conducted at 0, 25, and 75 ppm of VDC vapor. There were 86 rats/sex/level in the two-year portion of the sutdy. The parameters monitored were: body weight, food and water consumption (drinking water study only), haematology, clinical chemistries, cytogenetics of bone marrow cells (inhalation study only), mortality, terminal organ weights, and gross and histopathology. Based on interim kills and gross pathologic observations, the main conclusions are: increased dytoplasmic vacuolation of hepatocytes was seen in the livers of rats given 200 ppm VDC in drinking water or 25 or 75 ppm VDC vapor by inhalation; based on gross tumor count, tumour incidence in VDC-exposed rats was not greater than controls."

In 1977, in two similar articles, Lee et al. (1977 a, b) reported the results of a study, supported by the National Institute of Environmental Health Sciences (USA), on the carcinogenicity of vinyl chloride and VDC in Albino CD-1 mice and CD rats. In this project, mice and rats of both sexes were exposed by inhalation to 55 ppm of VDC, 6 hours daily, 5 days weekly. Similar groups of animals were kept as controls. The study lasted 12 months. In this experiment the authors reported that they had ob-

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Toxicity and carcinogenicity bioassays of vinylidene chloride. II. Chronic toxicity and carcinogenicity.

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served 6 lung adenomas among 35 treated male mice versus 1 among 26 controls, 3 liver angiosarcomas (2 in males and 1 in females) and 3 hepatomas (2 in males and 1 in females) from 70 treated mice, versus none from 62 controls. Two haemangiosarcomas (1 of the mesenteric nodes, and 1 in subcutaneous tissue) were found in two of 71 treated rats versus none of the 70 controls. Concerning the bronchiolar adenomas and the hepatomas in mice, the authors concluded that their significance is questionable, since the tumours may accur also in untreated animals (and probably in consideration of the small number of tested animals). As far as angiosarcomas are concerned, on the basis of our experience with long-term effects of VDC, this result was unexpected by us (Maltoni et al., 1977 a, b). The possibility of unwanted exposure to vinyl chloride used in parallel experiments was discussed at Bethesda "Conference on Comparative Metabolism and Toxicity of Vinyl Chloride Related Compounds" (1977).

The compatibility of a prolonged inhalatory exposure of mice to 55 ppm of VDC with a long survival does not parallel our experience on the acute toxicity in several strains of mice (Swiss, Balb/C, C3H, C57 Black), and on the chronic toxicity in Swiss mice, which appeared to bw much more sensitive to toxic effects of the monomer.

4. Planning, materials, and methods

The chambers for inhalation exposure were basically built of stainless steel and glass. The determination of VDC concentrations was carried out by gas chromatography.

For the ingestion experiments VDC was administered in olive oil by gavage with a stainless steel stomach tube.

VDC was supplied and analyzed by the Central Laboratory of Solvay (Brussels). The impurities and their levels in the VDC employed were as follows:

1,1-dichloroethylene (VDC)	999.5	g/kg
1,2-trans-dichloroethylene	0.4	"
acetone	0.1	"
methylene chloride	0.05	"
mono and dichloroacetylene	0.02	"

As stabilizer p-methoxyphenol at 200 ppm was used.

The experiments utilized Sprague-Dawley rats, Swiss mice and Chinese hamsters. All the animals, except the hamsters, had been bred in our Institute for years, and, whatever their use, were all examined at death by complete autopsy, giving us extensive information concerning their current pathology.

The animals were weaned and classified by sex when 4-5 weeks old, at which time they were numbered by ear punch and divided into groups by litter distribution. After weaning, the animals were given drinking water ad libitum and an adequate commercial diet. The animals were kept in groups of five in Makrolon* cages with tops made of stainless steel wire, but during the period of inhalatory treatment they were housed in groups of ten in stainless steel wire cages with a solid bottom of the same metal. A shallow layer of white-wood shavings served as bedding. The animals were kept in a temperature-controlled laboratory at 19-20 °C.

Five experiments were started around the same period. The plan of the experiments is given in tables 1 to 5.

*Polycarbonate

Experiment 1 (BT401) studied the effects on rats of inhalation exposure to 200 (then reduced, after two exposures, to 150 because of the strong toxic effects), 100, 50, 25, and 10 ppm of VDC, 4 hours daily, 4-5 days weekly, for 12 months. One group of animals served as control. 150 ppm was the highest tolerable dose by Sprague-Dawley rats for long-term exposure. From time to time the treatment was reduced from 5 to 4 times weekly because of early toxic effects in animals exposed to 150 ppm.

Experiment 2 (BT402) started with groups I, II, III, IV, V, and VI, and it was planned to study the effects on mice of inhalation exposure to the same range of VDC-doses as BT401. 25 ppm was found to be the highest tolerable dose by Swiss mice for long-term exposure. Doses of 200 and 100 ppm for 2 days, and of 50 ppm for 4 days (4 hours daily) caused death of a proportion of animals. When it appeared that exposure to 200, 100, and 50 ppm had to be withdrawn because of high mortality and severe toxic effects, the number of animals exposed to 25 ppm was enlarged by adding a supplementary group (IV/2), with its proper controls (group VII). In conclusion only two dose levels (10 and 25 ppm) were selected for this long-term study.

Experiment 3 (BT403) was designed to evaluate the effects of VDC on Sprague-Dawley rats by ingestion, at three dose levels: 20, 10, and 5 mg/kg body weight, once daily, 4-5 days weekly, for 52 weeks.

Experiment 4 (BT 404) was started to complement experiment BT403 with a lower dose (0.5 mg/kg body weight) once daily, 4-5 days weekly, for 52 weeks.

Experiment 5 (BOT405) was included to study the effects of VDC in Chinese hamsters at 25 ppm, which is the highest possible concentration for long-term exposure of mice and also one of the exposure levels of rats.

The animals were examined weekly, and weighed every 2 weeks during the period of treatment and monthly after the treatment was over. All the detectable gross pathological changes were recorded during the examination. All the animals were kept under observation until spontaneous death. Moribund animals were isolated, in order to avoid cannibalism.

A complete autopsy was carried out on each animal. Histological examinations were performed on the Zymbal glands, interscapular brown fat, salivary glands, tongue, lungs, liver, kidneys, spleen, stomach, different segments of the intestine, bladder, brain, bone marrow (sternum) and any other organs with pathological lesions. Furthermore, cytological examinations were carried out on the bone marrow of the femur. Histological sections were stained routinely with hematoxylin and eosin and, in particular cases, with Papanicolaou, Van Gieson, Mallory, and Gomory stains, silver stain, and Congo red. Cytological smears were stained with Giemsa and Papanicolaou stains.

Part of the results have been evaluated by statistical analysis (see Appendix).

5. Results

5.1. Chronic toxicity

The toxic effect was studied by histological examination of tissues and organs in animals that had died spontaneously. Therefore the observed changes had to be considered

as partly due to the treatment and partly due to spontaneous pathology and to immediate causes of death.

5.1.1. Rats

Regressive changes, such as hepatocytes vacuolisation, cloudy swelling, fatty degeneration (Fig. 1), necrobiosis, and necrosis were found in some animals, in treated as well as in control groups.

These changes were observed more frequently in rats exposed to 200-150 ppm by inhalation (57.6 %) than in controls (20.5 %).

5.1.2. Mice

Pathological changes were found in the liver and in the kidneys, both of control and treated animals.

The most frequent findings were regressive changes (hepatocytes and vacuolisation, cloudy swelling, fatty degeneration, necrobiosis and necrosis) and amyloidosis in the liver, and regressive changes (cloudy swelling and necrosis of tubular cells), amyloidosis of glomeruli, and chronic nephritis in the kidneys. The incidence of these lesions in the groups of animals treated with doses compatible with long survival (25 and 10 ppm) and controls is given in Tables 6 and 7. From these results no correlation emerges between the abovementioned changes and exposure to VDC.

A higher incidence of more pronounced regressive or phlogistic changes was found in residual parenchyma of kidneys with renal adenocarcinoma. In this situation it is not clear if these changes were due to treatment or to the presence of the tumor.

Areas of fibrosis, with or without calcium deposits (Fig. 2), were found in the liver of some of the few animals which survided treatment at the high doses of VDC. Such lesions were not noted in control animals. They should be interpreted as reparative scars, following severe necrosis of hepatic cells.

5.1.3. Hamsters

No particular changes were found in hamsters, neither in treated nor in control groups.

5.2. Carcinogenicity

5.2.1. Rats

Different kinds of tumours were observed in rats treated by inhalation and ingestion and in the control groups, the mammary ones being the most frequent.

The incidence of the different types of neoplasias, and the distribution of the different histotypes of mammary tumours and of some biological parameters related to them, are given in Tables 8-22.

In rats exposed to VDC by inhalation (Tables 8 & 11), and increase in the incidence of mammary tumours in general, but not of carcinomas, was observed among treated animals when compared with the control. Within the treated groups no dose/response relationship effect was found. No increase of mammary tumours was observed among rats to which VDC has been given by stomach tube (Tables 13, 16, 18, and 21) (see statistical evaluation appendix).

This phenomenon has been noted in other experiments studying compounds chemically related and also related to

VDC, suggesting that this increase of mammary tumours may be due to some "non-specific factors" connected to inhalation (such as olfactory stimulation with consequent stimulation of pituitary gland).

No other relevant findings have been recorded.

5.2.2. Mice

Because of the high early mortality in the groups treated with 200, 100 and 50 ppm, the results are mainly based on the groups treated at 25 and 10 ppm and on controls.

Various types of tumours were observed in mice, the most frequent ones being kidney adenocarcinomas, mammary tumours, pulmonary adenomas and leukemias.

The incidence of these different types of tumours, and data on the histotypes of mammary neoplasias are given in Tables 23-25.

5.2.2.1. Kidney adenocarcinomas

The most important finding was the onset of kidney adenocarcinomas in mice exposed to 25 ppm of VDC. This kind of tumour was also observed in one of the surfivors of the 50 ppm group. Such tumours were found neither in the 10 ppm group nor in the control groups, and they have not been noted in untreated Swiss mice of our breeding.

The tumours of the kidneys were almost exclusively in males (29 of the 30).

The kidney adenocarcinomas were found in left and right kidneys. In some cases they were bilateral (Fig. 3). Often in the same kidney they appeared to be multi-

centric. At the autopsy the tumours were often quickly detected as nodules of different sizes. Often they were observed in uniformly enlarged kidneys, and also in kidneys without any peculiar gross change.

Following different histological parameters, these tomours could present all the patterns occurring in current human pathology. The three different basis classical histotypes were observed, i.e. clear, granular and dark cell carcinomas; in dark cell carcinomas, the dytoplasm could be basophilic or strongly eosinophilic (Fig. 4-12). While some tumours were rather monomorphic, others presented pleomorphism of different degree: large cells with very voluminous nuclei were frequently found (Figs. 13-15). The adenocarcinomas were found to show tubular, papillary, cystopapillary, solid, and uniform arrangements (Figs. 16-18). Several of these different patterns in different combinations could be found in the same tumour. Two of these tumours were found with metastases, one in the lung, and one in the liver.

Hyperplasia and dyspiasia of tubuli were found in the kidneys of some treated male mice (Fig. 19 & 20).

5.2.2.2. Mammary tumours and lung adenomas

Mammary tumours, almost exclusively carcinomas, were found both in treated and in control groups. They were of the type usually observed in the untreated animals of our breed of mice. A higher incidence of these tumours was observed in the treated groups, without a dose/response relationship (Tables 23 & 25).

Pulmonary adenomas, some with cellular atypias, were found in treated and in control animals, with a higher incidence in the treated ones, without dose/ response relationship (Table 23).

Statistical analysis was performed to assess the significance of the differences in the incidence of mammary tumours and pulmonary adenomas in mice exposed to 25 and 10 ppm and in controls, also in relation to sex and age.

The important of analyzing these factors emerged from the following considerations:

(1) the spontaneous incidence of these tumours varied in the two sexes;

(2) these tumours were age-correlated, as are many other spontaneous tumours;

(3) in experiment BT402 the survival of mice exposed to 25 and 10 ppm was higher than survival of the control groups.

The data on mortality rates and the results of statistical analysis are fully reported in the Appendix. They show:

(1) There were some significant higher rates of mammary and pulmonary tumours in VDC-exposed groups when compared to the controls.

(2) When the incidence of these tumours was adjusted for survival rate, the significance of the difference between treated and control groups was reduced.

(3) No dose/response relationship could be calculated, either during the total time of the experiment or in different time intervals.

(4) Overall there was a clear fluctuation and imbalance of this trend in the different groups.

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In conclusion the direct relation of this effect to VDC treatment remains open.

5.2.2.3. Leukemias

No correlation between leukemias and VDC treatment was found.

5.2.3. Hamsters

Tumours (mainly uterine carcinomas) were found in treated as well as in the control groups. Their incidence was not increased by VDC treatment.

6 Related research in our and other laboratories

6.1. Acute toxicity

In acute experiments, when VDC was administered at relatively high doses to rats, it caused changes in the liver and plasma enzymes (Jenkins et al., 1972; Jäger et al., 1972 and 1973).

In rats exposed by inhalation to 200 ppm of VDC, Jäger et al. (1975) observed a massive mid-zonal hepatic necrosis with hepatic thrombosis and chromatolysis within 2 h after a 4-h exposure. Serum transaminase and sorbitol dehydrogenase were greatly elevated at 6 h. This effect in unfed rats was associated with glutathione (GSH) depletion.

An extensive study of acute toxicity was performed in our Institute (Maltoni et al., 1975, in press), on Sprague-Dawley rats and 4 strains of mice (Swiss, Balb/C, C3H, C57 Black). From this study it emerged that mice are more sensitive than rats, and that Swiss and Balb/C mice are

more sensitive than C3H and C57 Black mice. Apart from C3H mice, females appeared to be more resistant than males. Among the various effects observed the most prominent was necrosis, with cariorexis, in liver and in kidney. Such lesions appeared very marked and extensive in Swiss and Balb/C male mice.

6.2. Mutagenic effects

Greim et al. (1975) and Bartsch et al. (1975) obtained positive results with the Ames test. These authors pointed out some species-specific differences. VDC given alone showed no mutagenic effects on Salmonella strains. In adding a metabolic system of rat liver enzymes, small mutagenic effects could be seen. Using mouse-liver microsomes, the effects were several times greater.

These results parallel certain metabolic differences in the animal species. The ability of monoxygenases to form epoxides is twice as high in mice as in rats. In one of the further metabolic steps the epoxides can be transformed by means of epoxide hydratases to diols or other compounds: this enzyme system is seven times more reactive in rats than in mice (Oesch and Glatt, 1976); therefore, mice seem to produce much higher concentrations of reactive epoxides or their subsequent products of metabolism, which are postulated to be the possible direct active toxic components.

6.3. Cytogenetic effects

Balmer et al. Dow/MCA, 1975) could not detect any cytogenetic effects in rats exposed 6 weeks by inhalation to VDC in air at concentrations of 25 and 75 ppm. This was confirmed by BASF (1977), where in Chinese hamsters, exposed 5 days by inhalation to 100 ppm VDC, no increase

of chromosome aberrations in the bone marrow test could be found. After long-term exposure of 12 months to a concentration of 55 ppm Lee et al. (1978) could not find changes in the cytgenetic analysis of bone marrow test on rats as well as mice.

After a single oral dose of 217 mg/kg b.w. of VDC no statistically significant increase of the chromosome aberration rate was found (BASF, 1976).

On the basis of these results no cytogenetic effect of VDC could be found, either by long-term or by acute application of a high dose, in inhalation and oral studies with rodents.

6.4. Pharmacokinetic and metabolic studies

Jaeger et al. (1974) reported that the hepatotoxic effect of VDC is much higher in unfed rats than in fed rats, and that there is an inverse correlation between hepatotoxicity and the concentration of glutathione. These findings led to the hypothesis that the detoxification of VDC is primarily dependent upon the glutathione concentration.

Jaeger et al. (1977) pointed out that in unfed rats and fed rats exposed by inhalation to high doses of ^{14}C-VDC, ^{14}C radioactivity was found in various organs, particularly in kidney and in liver. The largest amount of total radioactivity was detected in the kidney of unfed rats.

^{14}C activity in liver cells was detected in mitochondrial, microsomal, and cytoplasmatic fractions. Significantly more radioactivity was found in all liver fractions of unfed rats. The administration of trichloropropane epoxide, an epoxide hydrase inhibitor, seemed to increase the toxicity of VDC significantly in unfed rats, the enhance-

ment of toxicity being proportional to the concentration of the inhibitor. This last result supports the hypothesis of the role of epoxide derivatives in toxicity of VDC.

McKenna et al. (1977) showed that in rats and mice exposed to ^{14}C-VDC, ^{14}C was covalently bound to macromolecules in liver and kidney of both species. The ^{14}C activity was higher in liver and in kidney of mice, in comparison to rats. The authors concluded that these data indicate an enhanced production of reactive metabolites of VDC in mice.

The data of Jaeger et al. and McKenna et al. bring further evidence that VDC toxicity does not correlate directly with the exposure per se, but is reflected in the balance of the amount of toxic metabolites and detoxification processes, which in turn are dependent upon many biological factors.

6.5. Epidemiological studies

In a recent study, published in November 1976, Ott et al. examined the mortality and the health control findings among 138 employees exposed to measured levels of VDC, ranging from 5 ppm to 75 ppm TWA (time weighted average), where vinyl chloride was not used as a second monomer. There were no findings in that study significantly related to VDC.

Hepatic damage was observed in 2 individuals with a positive history of ethanol consumption. The authors recommended "that additional epidemiologic data should be developed where exposure has taken place, with careful consideration given to obtaining an accurate history of alcohol consumption".

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In a similar study Thiess et al. (1977) reported mortality rates and health control findings of 629 employees exposed to VDC as well as to vinyl chloride and acrylonitrile. The VDC working-area concentrations were about 50 ppm (1955-1965), about 10 ppm (1965-1975), and 5-10 ppm after 1975. No significant increases in mortality or tumour incidence were found. Two lung carcinomas occurred at a very young age but with an exposure period of 14 and 25 months only (smoking habits unknown).

7 Conclusions

(1) Kidney adenocarcinomas were observed in Swiss (almost exclusively male) mice exposed by inhalation to VDC at 50 and 25 ppm. Under our experimental conditions, 50 ppm VDC was already a near lethal dose, and 25 ppm was the highest dose compatible with long survival of the treated animals.

No renal tumours were observed in mice exposed to 10 ppm VDC or in controls.

(2) Kidney adenocarcinomas were not observed in rats exposed to VDC by inhalation at doses from 150 to 10 ppm, or by ingestion (gavage) at doses from 20 mg to 0.5 mg/kg b.w., or in hamsters exposed by inhalation to 25 ppm.

(3) The increase of mammary tumours in rats exposed to VDC by inhalation was not dose-related, and therefore it is difficult to evaluate its specific relation to the administration of the monomer. This phenomen has been observed in other long-term inhalation bioassays.

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(4) The dependence of the increase of mammary tumours and lung adenomas in mice on VDC treatment still remains open and needs further clarification.

(5) In our experiments we did not observe liver angiosarcomas, either in treated rats or in mice. The animals used were of the same breed that is highly susceptible to induction of angiosarcomas by vinyl chloride.

(6) Our results have failed to confirm Viola's preliminary findings, which suggested that VDC was causing reticulosarcomas in rats.

(7) Under our experimental conditions, adenocarcinoma of kidney in mice was the only tumour specifically linked to VDC exposure.

(8) As far as this effect was concerned, there was a strong host influence: mice were more susceptible than rats and hamsters, and male mice much more than female mice.

(9) There was a clear cut direct relationship between the degree of susceptibility to acute toxid and carcinogenic effects in the different animals species and sexes studied.

(10) As a result of in vivo and in vitro studies it is probable that VDC is metabolized into more reactive compounds responsible for the toxic, mutagenic and carcinogenic effects of the monomer. The rate at which the actice metabolic compounds are formed and metabolized depends on the concentration of administered VDC and on the metabolic pathways in the tested animals, which appear to be strongly influenced by species and sex, as well as by other factors.

(11) The mice used had the appropriate metabolic conditions for indicating the oncogenic potentiality of VDC.

(12) From a scientific point of view, the results of the studies on toxic, mutagenic, and carcinogenic effects of VDC and on its metabolism represent an exceptional integration of experimental multidisciplinary information.

(13) We think that further investigations are needed in biological, biochemical, epidemiological, and medical fields, in order to

(a) further investigate the roles of species, strain, and sex on the pathological effects of VDC;

(b) learn more about the metabolism, with particular regard to active metabolic compounds, and the biological factors influencing the metabolic pathways;

(c) collect all possible epidemiological and medical data on occupationally exposed groups, which together with experimental results will provide the background for risk assessment.

8 Summary

The present report deals with the results of a wide array of correlated and integrated experiments aimed at the study of the long-term effects of VDC, with particular regard to carcinogenicity. The monomer is employed in the production of polymers whose major use is in the manufacturing of flexible packaging for food.

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The monomer was tested by inhalation, in Sprague-Dawley rats (200-150, 100, 50, 25, 10 ppm), Swiss mice (200, 100, 50, 25, 10 ppm), and Chinese hamsters (25 ppm), and by ingestion in rats (at the doses of 20, 10, 5, 0.5 mg/kg body weight, in olive oil, by stomach tube).

The treatment was carried out 4-5 times weekly, for 1 year, with the exception of the groups of mice, treated by inhalation, at 200, 100 and 50 ppm, in which it was withdrawn after a few days, because of the excessive acute toxicity. 25 ppm is therefore the highest tested dose, compatible with a long-term treatment, by inhalation in mice.

The most important result was onset of kidney adenocarcinomas in mice exposed by inhalation at 50 and 25 ppm. Male mice appeared to be more susceptible than females. This tumour was not observed in mice exposed by inhalation at 10 ppm VDC or in the other treated animal species.

Increase of mammary tumours in rats and mammary tumours and lung adenomas in mice were found following inhalatory exposure to VDC. The lack of dose/ response relationship, the results of statistical analysis, and biological information from these as well as from other correlated experiments leave the problem of the correlation between these tumours and inhalation exposure to VDC or other monomers still open.

The available data based upon the studies performed in our and other laboratories show good correlation among the results of studies on carcinogenicity, toxicity, mutagenicity, and metabolism of VDC.

On the basis of our present knowledge on VDC toxicity and carcinogenicity, the need for further experimental and

epidemiological investigations for risk assessment has been suggested.

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